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Comparative effectiveness of endovascular versus surgical revascularization for acute lower extremity ischemia

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Objective: **Thrombolysis and open surgical revascularization are current options for the treatment of acute limb ischemia (ALI). Despite the several randomized controlled trials comparing the two options, no single treatment can yet be recommended as a universal initial management of ALI. The purpose of this study was to evaluate contemporary endovascular and surgical revascularization for ALI.**

Methods: **Consecutive patients with ALI treated with endovascular revascularization (ER) or open revascularization (OR) between 2005 and 2011 were identified and reviewed. Procedural success and outcomes were compared between the two groups. Limb salvage and survival were assessed by time-to-event methods, including Kaplan-Meier estimation and competing-risks regression models.**

Results: **A total of 154 limbs were treated in 147 patients in the ER group, compared with 326 limbs in 296 patients in the OR group. The mean follow-up was 14 ± 18.5 months. The majority of patients presented with Rutherford II ischemia (83% for OR, 90% for ER). In Rutherford II patients, technical success was achieved in 90.7% of the OR group vs 79.9% of the ER group ($P = .002$), with amputation rates of 10.0% vs 7.2% ($P = .35$) at 30 days and 16.3% vs 13.0% ($P = .37$) at 1 year, respectively. In Rutherford II patients with failed bypass graft, technical success rate was 95.0% (OR) vs 75.0% (ER) ($P = .001$), whereas the amputation rate was 6.3% vs 15.38% ($P = .13$) at 30 days and 24.1% vs 23.1% ($P = .90$) at 1 year, respectively. The overall 30-day mortality rate was 13.2% (OR) and 5.4% (ER) ($P = .012$). Overall amputation rates were 13.5% (OR) vs 6.5% (ER) at 30 days ($P = .023$) and 19.6% (OR) vs 13.0% (ER) at 1 year ($P = .074$). The primary patency rate was 57% (OR) and 51% (ER) at 1 year ($P = .74$). Predictors of limb loss by life-table analysis included coronary artery disease (hazard ratio [HR], 2.0; $P = .007$) and Rutherford category III (HR, 19.0; $P < .001$). Predictors of death by life-table analysis included age (HR, 1.03; $P < .001$), end-stage renal disease (HR, 7.28; $P < .001$), cancer (HR, 1.65; $P = .005$), and chronic obstructive pulmonary disease (HR, 1.61; $P = .005$).**

Conclusions: **In patients presenting with class II ALI, ER or surgical OR resulted in comparable limb salvage rates. Although technical success is higher with OR for patients presenting with failed bypass grafts, the amputation rates are comparable. Overall mortality rates are significantly higher at 30 days and 1 year in the OR group. (J Vasc Surg 2015;61:147-54.)**

Large randomized controlled trials have reported several advantages to thrombolysis for the treatment of acute limb ischemia (ALI), including decreased amputation rates, improved amputation-free survival, shorter hospital admission,[1] and decreased subsequent requirements for surgical revascularization.[2] Consequently, catheter-directed thrombolysis (CDT) has been proposed as an alternative to surgical revascularization as an initial treatment of ALI of embolic or thrombotic etiology.[3]

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The development of advanced thrombolysis techniques such as pharmacomechanical thrombolysis (PMT) and the use of newer pharmacologic agents have helped achieve a more complete and faster clot lysis while shortening the duration of lysis.[4] However, the risk of life-threatening bleeding,[5] including intracranial hemorrhage,[1] and the necessity for intensive care monitoring remain serious tradeoffs to be considered in use of thrombolytic therapy.

Given the absence of contemporary outcomes comparing surgery with lysis by current devices and pharmacologic agents for the treatment of ALI,[6] the aim of this study was to assess the comparative effectiveness of surgical revascularization vs CDT with or without PMT in terms of clinical efficacy and safety as initial options in the treatment of thromboembolic acute lower extremity ischemia.

METHODS

This study is a retrospective single-institutional review of the prospectively maintained vascular registry at the University of Pittsburgh Medical Center. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh. No study specific consent was

required as no patient identifiers were collected and the study received an exempt status. All patients gave informed consent to undergo the procedures listed.

Patients. The study included all patients with lower extremity ALI who underwent endovascular revascularization (ER) or open revascularization (OR) at the University of Pittsburgh Medical Center from January 2005 through May 2011. All procedures were performed by vascular surgeons. Procedural success, complications, and limb and overall outcome data were compared between the two groups.

Only patients with ALI due to embolism or thrombosis of a native artery, bypass graft, or previous stent were considered in the study. Blue toe syndrome and acute ischemia secondary to trauma or dissection were excluded. Severity of ischemia was assessed according to Rutherford's clinical categories of ALI.[7] If Rutherford categorization was not clearly reported in the patient's chart, it was derived by two authors on the basis of the reported sensory/motor affection and its severity as well as the presence or absence of Doppler signals on pedal vessels, tissue loss, rigor, or gangrene on presentation. Patients without reported Rutherford categorization and those missing one or more criteria for the proper categorization were classified as "unknown severity." The pedal runoff was evaluated angiographically at the initiation and completion of thrombolysis by assessing the patency of the dorsalis pedis, posterior tibial, and peroneal collateral vessels in the foot.

Procedures. For the purpose of analysis, patients were segregated into the ER and OR groups according to the type of the procedure needed to treat the first acute ischemic incident during the study period. Excluding technical failures requiring crossover, if the initial procedure was followed by another procedure of a different revascularization type, the latter procedure was considered an adjuvant treatment and did not disqualify the patient from the initial categorization.

The choice of the initial revascularization or subsequent adjuvant treatment was at the operator's discretion. However, the revascularization approach was standardized on the basis of the ALI etiology (eg, surgical thrombectomy for atrial fibrillation [AF] patients vs thrombolysis for small-vessel emboli and thrombosed bypass vein graft or stent in patients presenting with Rutherford I or II ischemia). Timing of the revascularization procedure relied mainly on the severity of ischemia on presentation. Mild degrees of ischemia allowed a longer time window for basic workup and patient optimization. All operative notes and imaging were reviewed for technical details and to assess for thrombus distribution, response to therapy, and complications.

In general, CDT was conducted with standard wire and catheter techniques to embed a multisidehole catheter (Cragg-McNamara; ev3 Endovascular Inc, Plymouth, Minn; or Unifuse; AngioDynamics, Latham, NY) into the thrombosed arterial segment. If thrombosis extended to the tibial vessels, a Katzen infusion wire (Boston Scientific, Natick, Mass) was also used as a coaxial system. Recombinant tissue plasminogen activator (rtPA; Genentech, Inc, San Francisco, Calif) was the sole lytic agent used. A bolus of 2 to 6 mg of rtPA was delivered into the thrombus, followed by an infusion at a rate of 0.25 to 1.00 mg/h. Unfractionated heparin was given through the access sheath at a rate of 500 units/h to prevent pericatheter thrombosis. Follow-up angiography was typically performed 6 to 12 hours later on the basis of the clinical response.

PMT with the AngioJet catheter (MEDRAD, Inc, Warrendale, Pa) was more likely to be used in fresh clot that was less than 2 weeks old, primarily in thrombosed femoropopliteal stents, or for residual thrombus after CDT and was typically avoided in tibial vessels. PMT was initially used in power pulse mode with 6 to 10 mg of rtPA, then in regular thrombectomy mode after 12 to 15 minutes of dwell time. Adjuvant CDT was performed on the basis of the presence of residual thrombus.

Outcomes. The end points for analysis were technical success, incidence of postoperative complications, length of hospital stay, loss of primary patency, loss of assisted primary patency, and loss of secondary patency as well as amputation and mortality rates at 30 days and 1 year. Mortality rates were analyzed on a patient level, but other outcomes were analyzed on a limb level.

Mortality, incidence of complications, and patency rates were calculated for all patients for ER and OR, whereas technical success and amputation rates were calculated for all patients as well as for patients in each ischemia severity class. Rates specific to Rutherford II class were further stratified by the cause of ischemia.

Unplanned return to the operating room was reported as a complication and included any unscheduled return to the operating room within 30 postoperative days (eg, amputations, débridement of infected wound, hematoma evacuation, repair of a pseudoaneurysm, delayed fasciotomy, or another attempt of revascularization).

Because many OR patients did not have preoperative or completion angiograms, surgical intervention was considered technically successful when a palpable pulse or biphasic Doppler signals were detected over at least one of the pedal vessels at the completion of the procedure. Return of monophasic Doppler pedal signals after OR procedures was not necessarily considered a technical success in this study, unless it was positively ascertained that this is the patient's baseline. Loss of pulse or Doppler signals at any time point after leaving the operating room did not count as a technical failure but rather signified the end of the primary patency of that procedure. For ER procedures, technical success was achieved when in-line blood flow was restored to the foot (or to the ankle through a patent peroneal artery or large collateral vessel) without requirement for surgical conversion.

Patency rates were calculated for the initial revascularization procedure and according to published descriptions.[7] Recognizing the heterogeneity between the two groups in terms of severity of ischemia on presentation, the limb-level comparisons of outcomes were restricted to patients presenting with Rutherford II ischemia.

Statistical analysis. Patient demographics, comorbidities, cause and severity of ischemia, and complications

were compared between the two treatment groups by the χ^2 test and *t*-test for categorical and intervally scaled variables, respectively. Patency rates, limb salvage, and survival were assessed by time-to-event methods, including Kaplan-Meier estimation and competing risk-regression models. Multivariate analysis was performed by logistic or Cox proportional hazard regression models to identify predictors of technical success, limb loss, loss of patency, and death. That was done by a full regression model with all candidate predictors, followed by a stepwise regression where all predictors with a $P < .1$ were retained. Variables of stepwise selection with $P < .05$ were considered statistically significant.

RESULTS

Patient population. A total of 154 limbs (147 patients) in the ER group were compared with 326 limbs (296 patients) in the OR group. Patient characteristics, severity of ischemia, and indication for intervention are presented in Table I. ER patients were younger (66 vs 70 years; $P = .003$) but more likely to be smokers and to have a history of coronary artery bypass grafting and chronic renal insufficiency. OR patients were more likely to have AF or rhabdomyolysis on presentation. Otherwise, no significant differences were detected between the two groups.

Cause and severity of ischemia. There were significant differences between the two groups in terms of cause of ischemia (Table I); cardiac embolism was more common in the OR group, whereas failed stent was more common in the ER group. Although presentation with a failed bypass graft was almost equally prevalent in both groups (31% in OR vs 36% in ER; $P =$ not significant [NS]), 80% of the failed grafts were prosthetic in the OR group compared with 45% in the ER group ($P < .001$), whereas 10% were vein grafts in the OR group compared with 52% in the ER group ($P < .001$).

Despite the differences in the number of ischemic limbs between the two groups in each severity category, the majority of limbs were classified on presentation as Rutherford IIa (41% in OR vs 70% in ER; $P < .001$) or IIb (42% in OR vs 20% in ER; $P < .001$; Table I).

Procedures performed. In the OR group, 293 thromboembolectomies were done (144 femoral, 41 popliteal or tibial, 37 multilevel, and 71 for thrombosed bypass grafts) in addition to 107 bypass grafts (54 infrainguinal, 34 inflow, and 19 femorofemoral crossover bypass grafts) and 67 endarterectomies (51 femoral, nine popliteal, three tibial, three iliac, and one aortic). Hybrid procedures included 34 combined balloon angioplasty and stenting (23 iliac, five superficial femoral, three popliteal, and three graft stenosis) and 22 balloon angioplasty only (six iliac, six popliteal, six tibial, three graft stenosis, and one superficial femoral artery).

In the ER group, 83 limbs received CDT only, 15 received PMT only, and 56 received a combination of CDT and PMT.

Table I. Patient characteristics, severity of ischemia, and indications for intervention

	OR group, No. (%)	*ER group, No. (%)*	P *value*
No. of patients	296	147	
No. of limbs	326	154	
Age, years, mean ± SD	70.4 ± 14.4	65.9 ± 15.2	.003[a]
Male	164 (55.4)	86 (58.5)	.54
Smoking			
None	150 (50.7)	37 (25.2)	<.001
Current	93 (31.4)	66 (44.9)	.006
Former	50 (16.9)	42 (28.6)	.003
Unknown	3 (1.0)	2 (1.4)	
Comorbidities			
Coronary artery disease	144 (49.0)	79 (55.2)	.22
End-stage renal disease/ dialysis	12 (4.1)	6 (4.2)	.96
Congestive heart failure	57 (19.4)	28 (19.6)	.96
Chronic obstructive pulmonary disease	86 (29.1)	33 (22.4)	.17
AF	114 (38.5)	32 (21.8)	.001
Coronary artery bypass graft	49 (16.6)	37 (25.2)	.02
Stroke	48 (16.2)	18 (12.2)	.31
Cancer	67 (22.6)	32 (21.8)	.92
Hypertension	234 (79.1)	111 (75.5)	.73
Dyslipidemia	133 (44.6)	64 (43.5)	.98
Rhabdomyolysis	14 (4.7)	1 (.7)	.03
Chronic renal insufficiency[b]	39 (13.2)	31 (22.0)	.02
Diabetes	91 (30.7)	57 (38.8)	.06
Cause of ischemia[c]			
Cardiac embolism	86 (26.4)	14 (9.1)	<.001
Native artery thrombosis	93 (28.5)	37 (24.0)	.07
Failed stent	32 (9.8)	41 (26.6)	<.001
Failed bypass	100 (30.7)	56 (36.4)	.21
Prosthetic graft[d]	80 (80)	25 (44.6)	<.001
Vein graft[d]	10 (10)	29 (51.8)	<.001
Unspecified graft type[d]	10 (10)	2 (3.6)	.15
Thrombosed peripheral aneurysm	18 (5.5)	6 (3.9)	.45
Aortoiliac embolism	14 (4.3)	8 (5.2)	.66
Distribution by severity			
Rutherford I	4 (1.2)	15 (9.7)	<.001
Rutherford IIa	132 (40.5)	108 (70.1)	<.001
Rutherford IIb	138 (42.3)	31 (20.1)	<.001
Rutherford III	12 (3.7)	0 (0)	.003
Unknown	40 (12.3)	0 (0)	<.001

AF, Atrial fibrillation; *ER,* endovascular revascularization; *OR,* open revascularization; *SD,* standard deviation.
[a]Logistic regression of procedure onto age.
[b]Baseline serum creatinine level >1.2 g/dL.
[c]Some cases had multiple causes of ischemia.
[d]Percentages are based on the total failed bypass.

Technical success. In the ER group, the mean duration of lysis was 25.5 hours for CDT and 23.6 hours for PMT. Thirty limbs in the ER group failed thrombolysis because of inadequate response in 26 limbs (13 of them were treated with successful bypass surgery), intraoperative bleeding events in three limbs, and failure to cross the thrombosed vessel in one limb. Patients for whom lysis failed and who were not candidates for bypass surgery

Table II. Technical success rates stratified by severity

	OR group (n = 326)		*ER group (n = 154)*		
	No.	*%*	*No.*	*%*	P *value*
All limbs	287/326	88.04	124/154	80.52	.028
Category I	4/4	100.00	13/15	86.67	.99
Category IIa	129/132	97.73	86/108	79.63	<.001
Category IIb	116/138	84.06	25/31	80.65	.644
Category II (a + b)	245/270	90.74	111/139	79.86	.002
Failed bypass	75/80	94.94	39/52	75.00	.001
Prosthetic	61/63	96.83	21/24	87.50	.13
Vein	5/7	71.43	16/26	61.54	.99
Failed stent	26/26	100.00	31/38	81.58	.04
Embolism	77/87	88.51	17/21	80.95	.47
Cardiac embolism	66/75	88.00	12/13	92.30	.99
Aortoiliac embolism	11/12	91.67	5/8	62.50	.26
Native artery thrombosis	67/76	88.16	24/26	92.31	.73
Thrombosed peripheral aneurysm	13/15	86.67	2/6	33.33	.031
Category III	4/12	33.33	—	—	—

ER, Endovascular revascularization; *OR*, open revascularization.

Table III. Thirty-day and 1-year amputation rates

	OR group		*ER group*		
Amputation rate	*No.*	*%*	*No.*	*%*	P *value*
30-day					
All limbs	44/326	13.50	10/154	6.49	.023
Category II (a + b)	27/270	10.0	10/139	7.19	.349
Failed stent	2/26	7.69	1/38	2.63	.561
Failed bypass	5/79	6.33	8/52	15.38	.134
Thrombosed peripheral aneurysm	2/15	13.33	1/6	16.67	.999
Embolism	7/87	8.05	0/21	.00	.341
Native artery thrombosis	11/76	14.47	0/26	.00	.061
1-year					
All limbs	64/326	19.63	20/154	12.99	.074
Category II (a + b)	44/270	16.30	18/139	12.95	.371
Failed stent	7/26	26.92	4/38	10.53	.104
Failed bypass	19/79	24.05	12/52	23.08	.898
Thrombosed peripheral aneurysm	2/15	13.33	1/6	16.67	.999
Embolism	7/87	8.05	1/21	4.76	.999
Native artery thrombosis	14/76	18.42	1/26	3.85	.107

ER, Endovascular revascularization; *OR*, open revascularization.

required major amputation (10 limbs); one was treated with observation, whereas four patients (six limbs) died.

The overall technical success rate was better with OR (88%) than with ER (81%; $P = .028$; Table II). The technical success rate was also improved in limbs treated for Rutherford II ischemia and was 91% for OR vs 80% for ER ($P = .002$). Stratification in Rutherford II patients by the cause of ischemia showed that OR continued to result in improved technical rates compared with ER when ALI was caused by failed bypass graft (95% vs 75%; $P = .001$), failed stent (100% vs 82%; $P = .04$), or thrombosed peripheral aneurysm (87% vs 33%; $P = .031$).

Complications. OR was associated with a higher incidence of wound infection (9% vs 0.7%; $P < .001$), rethrombosis (14.7% vs 1.3%; $P < .001$), fasciotomy (29.1% vs 7.3%; $P < .001$), or unplanned return to the operating room (25.5% vs 1.3%; $P < .001$) compared with ER. Also, OR had a higher incidence of reversible postoperative acute renal failure (12% vs 4%; $P = .005$) and new-onset postoperative hemodialysis (4% vs 0.7%; $P = .04$) as well as a more prolonged hospital stay compared with ER (11.5 ± 12 vs 8 ± 7 days; $P = .002$). On the other hand, ER was associated with a higher incidence of systemic bleeding events than OR was (5.8% vs 0%; $P < .001$).

Limb loss and survival. The overall 30-day amputation rate was significantly higher with OR (13.5%) than with ER (6.5%; $P = .02$; Table III and Fig 1). Excluding Rutherford III patients, rates were 11.5% for OR vs 6.5% for ER ($P = .09$). Amputation rates specific to patients presenting with Rutherford II ischemia were comparable between the two groups (10% for OR vs 7% for ER; $P = .35$), and this remained true when stratified by cause of ischemia

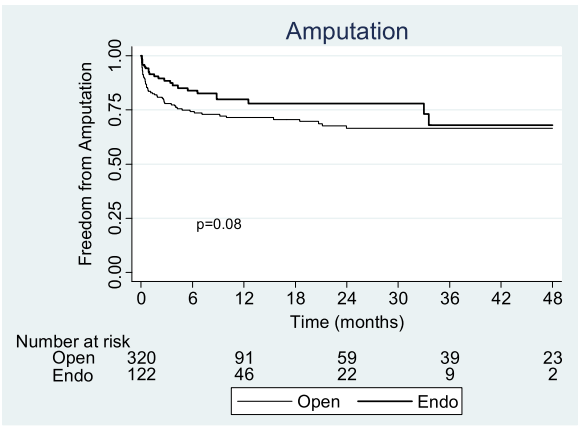

Fig 1. Kaplan-Meier survival curve: Amputation-free survival (limb-based analysis).

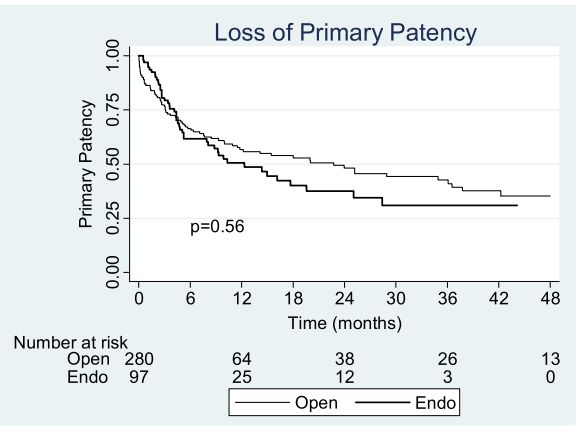

Fig 3. Kaplan-Meier survival curve: Primary patency (limb-based analysis).

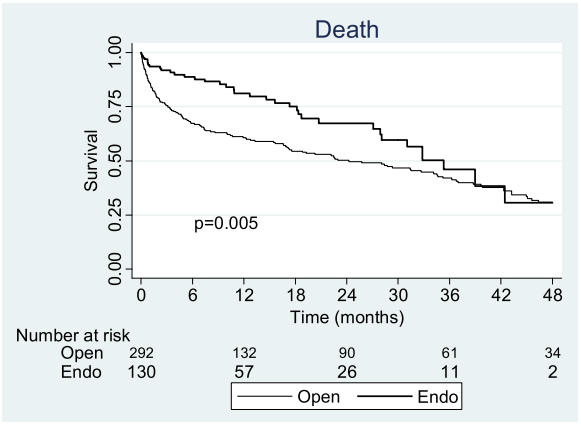

Fig 2. Kaplan-Meier survival curve: Survival analysis (patient-based analysis).

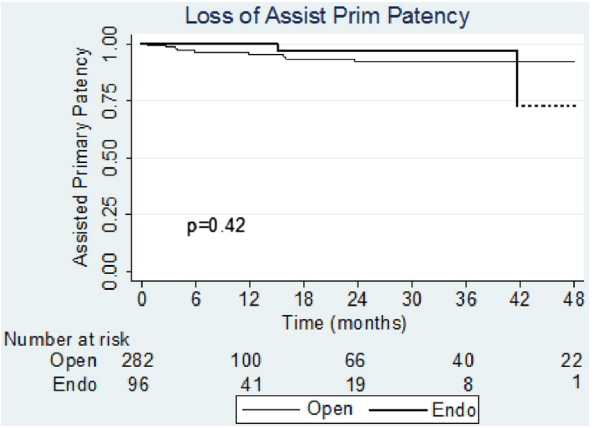

Fig 4. Kaplan-Meier survival curve: Assisted primary patency (limb-based analysis).

in this subgroup of patients. At 1 year, no significant differences were noted between the OR and ER groups in the overall amputation rates or in rates specific to Rutherford II patients as well.

In Rutherford II patients, despite the fact that amputation rates were comparable between ER and OR, there was an observed trend toward improved limb salvage at 30 days and 1 year with ER compared with OR, specifically in patients presenting with failed stent or native artery thrombosis. In contrast, OR showed a trend toward better limb salvage at 30 days compared with ER, specifically for patients presenting with failed bypass graft.

The overall mortality rates (Fig 2) were significantly lower with ER than with OR at 30 days (5.4% vs 13.2%; $P = .012$), 1 year (12.9% vs 33.8%; $P < .001$), and 2 years (18.7% vs 40.5%; $P < .001$).

Patency rates. The mean follow-up time was 14 months (range, 1-92 months). The primary patency rates were comparable between OR and ER at 1 year (57% and 51%, respectively; $P = .74$) and 2 years (48% and 38%, respectively; $P = .38$). The primary-assisted patency rates for OR and ER (96% and 100% at 1 year, 92% and 97% at 2 years, respectively; $P =$ NS) and secondary patency rates (96% and 91% at 1 year, 92% and 89% at 2 years, respectively; $P =$ NS) were also comparable (Figs 3 to 5).

Predictors of technical success. Predictors of technical success were sought to help in the clinical decision making based on patient presentation, etiology of ischemia, and patient anatomy. Multivariable analysis of all the study patients showed that ER (odds ratio [OR], 0.2; $P = .001$) and Rutherford III ischemia on presentation (OR, <0.01; $P = .001$) were less likely to achieve technical success compared with OR and less severe ischemia (Table IV). On the other hand, the presence of any patent pedal outflow was a significant predictor for technical success (OR, 6.0, $P < .001$ for one vessel; OR, 6.9 and $P = .002$ for two vessels; OR, 7.7 and $P = .012$ for three vessels). Other predictors used in the regression model, such as comorbidities, etiology of ischemia, prosthetic bypass, vein bypass, or failed stent, were not significant predictors of the technical outcome.

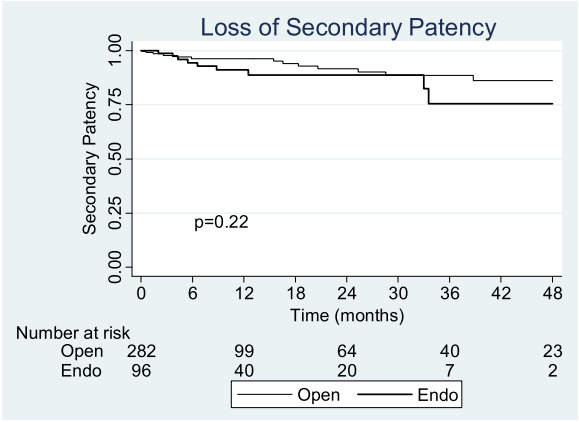

Fig 5. Kaplan-Meier survival curve: secondary patency (limb-based analysis).

Table IV. Predictors of technical success

Variable	*OR*	*95% CI*	P *value*
ER	0.19	0.072-0.513	.001
Comorbidities			
Age	1.03	1.005-1.058	.019
Cancer	0.44	0.181-1.076	.072
Pedal outflow[a]			.001
1 vessel	5.95	2.342-15.127	<.001
2 vessels	5.88	1.917-18.060	.002
3 vessels	7.69	1.554-38.109	.012
Severity of ischemia[b]			.001
Category IIa	0.60	0.101-3.571	.575
Category IIb	0.24	0.035-1.581	.137
Category III	<0.01	<0.001-0.103	.001

CI, Confidence interval; *ER,* endovascular revascularization; *OR,* odds ratio.
[a]Reference category is zero.
[b]Reference category is Rutherford I category.

Predictors of loss of primary patency. Rutherford III ischemia on presentation was a strong predictor for loss of primary patency (hazard ratio [HR], 6.2; $P = .02$). Other significant predictors included failed stents and failed prosthetic or vein bypass grafts as causes of ischemia (Table V). Irrespective of the severity of ischemia on presentation, neither the type of revascularization nor the number of pedal outflow vessels was found to predict for the loss of primary patency.

Predictors of limb loss. The only significant predictors for limb loss were presentation with Rutherford III ischemia (HR, 19.3; $P < .001$) and coronary artery disease (HR, 1.97; $P = .007$; Table VI). In all study patients, the type of revascularization (ER vs OR) and the cause of ischemia were not predictors for limb loss.

Predictors of mortality. Factors that conferred the highest risk for overall mortality included end-stage renal disease and advanced ischemia (Rutherford IIb and III; Table VII). Age, cancer, and chronic obstructive pulmonary disease were also associated with a significant risk for mortality.

Table V. Predictors of loss of primary patency

Variable	*HR*	*95% CI*	P *value*
Endovascular intervention	0.850	0.560-1.290	.430
Comorbidities			
CAD	1.580	1.110-2.250	.020
Cause of ischemia			
Failed stent	2.410	1.571-3.699	<.001
Failed bypass			.004
Prosthetic	1.686	1.131-2.514	.010
Vein	2.433	1.263-4.688	.010
Severity of ischemia[a]			.002
Category IIa	0.615	0.289-1.307	.210
Category IIb	0.642	0.290-1.423	.280
Category III	6.182	1.497-25.522	.020

CAD, Coronary artery disease; *CI,* confidence interval; *HR,* hazard ratio.
[a]Reference category is Rutherford I category.

Table VI. Predictors of limb loss

Variable	*HR*	*95% CI*	P *value*
Endovascular intervention	1.061	0.624-1.803	.827
Comorbidities			
ESRD/dialysis	2.349	0.890-6.200	.085
CAD	1.970	1.208-3.214	.007
CHF	0.482	0.242-0.959	.037
Severity of ischemia[a]			<.001
Category IIa	1.179	0.272-5.108	.826
Category IIb	3.418	0.792-14.742	.099
Category III	19.305	3.699-100.760	<.001

CAD, Coronary artery disease; *CHF,* congestive heart failure; *CI,* confidence interval; *ESRD,* end-stage renal disease; *HR,* hazard ratio.
[a]Reference category is Rutherford I category.

Table VII. Predictors of mortality

Variable	*HR*	*95% CI*	P *value*
Endovascular intervention	0.687	0.447-1.055	.086
Comorbidities			
Age	1.031	1.018-1.043	<.001
Cancer	1.646	1.160-2.336	.005
ESRD/dialysis	7.278	3.577-14.809	<.001
CRI	1.449	0.973-2.157	.068
COPD	1.609	1.154-2.245	.005
Severity of ischemia[a]			.001
Category IIa	5.973	0.772-46.237	.087
Category IIb	7.995	1.030-62.078	.047
Category III	38.675	4.617-323.971	.001

CI, Confidence interval; *COPD,* chronic obstructive pulmonary disease; *CRI,* chronic renal insufficiency; *ESRD,* end-stage renal disease; *HR,* hazard ratio.
[a]Reference category is Rutherford I category.

DISCUSSION

The benefits of thrombolysis as an initial treatment of ALI were reported in a number of trials comparing OR and ER of acutely ischemic limbs.[1,2,8] However, the heterogeneity between those studies made it difficult to directly compare the treatment outcomes or to apply them to current clinical practice.

We also found significant differences in our study between the OR and ER groups in terms of prevalence of the different causes of ischemia as well as the severity of ALI on presentation. We therefore focused in our limb-level comparisons on patients presenting with Rutherford IIa or IIb categories and on subgroup analyses of individual causes of ischemia to have comparable groups. Indeed, patients presenting with Rutherford II (IIa and IIb) ischemia composed the majority of the ischemic limbs in our study (82.8% of the OR group vs 90.2% of the ER group), allowing us to compare the treatment outcomes.

In this study, the overall 30-day amputation rates were lower in the ER group than in the OR group (6.5% vs 13.5%; $P = .023$), and these were similar to the amputation rates previously reported in the Surgery vs Thrombolysis for Ischemia of the Lower Extremity (STILE) trial (5.7% and 17.9%, respectively).[1] At 1 year, the overall amputation rate in the ER group (13%) was comparable to that reported in the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial (15%)[2]; however, the amputation rate in our OR group was higher (19.6%) than the rate for OR reported in the TOPAS (13.1%)[2] or Rochester (18%)[8] trial. This can be explained by the fact that both trials excluded patients with advanced limb ischemia, whereas some of our OR limbs were treated for Rutherford III ischemia. Moreover, 40 limbs (12.3%) of the OR group could not be classified into any Rutherford category because of the retrospective nature of the analysis or the presence of a coexisting condition that prevented categorization (eg, remote history of paralysis, compromised level of consciousness, patients transferred under anesthesia). Some of those ischemic limbs of unclassified severity could have had Rutherford III ischemia, which confers a significantly higher amputation rate.

On the other hand, the amputation rates in patients treated for Rutherford II ischemia were comparable between the ER and OR groups at 30 days (7% vs 10%, respectively; $P = $ NS) and at 1 year (13% vs 16%, respectively; $P = $ NS). This is also comparable to the 1-year amputation rates of the thrombolysis and surgical arms in both the TOPAS (15% vs 13.1%)[2] and Rochester (18% vs 18%)[8] trials. In agreement with this observation, the multivariate analysis in the present study showed that the type of revascularization with ER or OR did not predict for limb loss in patients presenting with Rutherford II ischemia, suggesting that either approach can achieve similar limb salvage in general.

However, this general observation may not hold true in comparing limb salvage on the basis of the etiology of limb ischemia. Consequently, we further stratified the amputation rates of Rutherford II patients by the etiology of ischemia. Although this stratification failed to show a significant difference between ER and OR (at 30 days or 1 year), ER showed a trend toward better limb salvage compared with OR, specifically in patients with failed stent (amputation rate of 2.6% vs 7.7% at 30 days, $P = .561$; and 10.5% vs 26.9% at 1 year, $P = .104$) or native artery thrombosis (amputation rate of 0% vs 14.5% at 30 days, $P = .061$; 3.9% vs 18.4% at 1 year, $P = .107$). In contradistinction, the STILE trial showed a higher rate of amputation with thrombolysis for nonembolic native artery occlusion compared with surgery.[9] However, this may reflect outcomes of subacute ischemia because the majority of STILE patients had chronic symptoms (44% with symptoms for 1 month or more and 26% for 2 months or more vs 30% with symptoms within 14 days). The lack of agreement between those results and ours may imply that ER can be more useful in the setting of acute arterial occlusion.

In patients with failed bypass grafts, OR showed a favorable trend for limb salvage at 30 days (amputation rate of 6.3% vs 15.4%; $P = .0134$), but this was not maintained at 1 year (1-year amputation rate of 24% vs 23%; $P = .898$). In contrast, a post-study analysis of STILE patients with acute graft occlusion showed that thrombolysis had a significantly reduced 1-year amputation rate compared with surgery.[10] In that analysis, thrombolysis was found to be most beneficial in acutely occluded vein grafts, whereas thrombolysis of occluded prosthetic grafts was associated with increased morbidity.

In this study, vein grafts represented only 25% of all graft occlusions. The limited frequency of vein graft occlusion, which might derive better outcomes with thrombolysis, may have contributed to the reduced limb salvage with ER relative to OR in patients with failed bypass. Although the benefit of OR was not maintained in our study, the observed short-term benefit of OR suggests that surgical revascularization may be the preferred option for the treatment of ALI secondary to failed bypass grafts, at least for patients with failed prosthetic grafts.

In addition, whereas the proportion of patients presenting with native artery thrombosis and vein or prosthetic graft occlusion was equally distributed in patients treated with ER (24%, 16%, and 19%, respectively), this was not the case for patients treated with OR (29%, 3%, and 25%, respectively). As such, this allowed a reliable comparison between the amputation rates associated with those three causes of ischemia in patients treated with ER, which showed that risk of limb loss was not different by the type of vessel.[4] This comparison was not undertaken in patients treated with OR, given the limited representation of patients with failed vein bypass graft.

Limb ischemia from AF represented 26% of OR and 9% of ER in all patients (29% and 9% in Rutherford II patients). The higher prevalence of AF embolism treated with OR might have biased the overall amputation rates, given the generally simpler operation required for revascularization. As such, cause-specific rates were calculated to minimize such a bias, allowing us to estimate amputation rates for each category (failed stent, failed bypass graft, native artery thrombosis). What was interesting to note, however, is that patients presenting with an AF embolus and treated with ER were able to achieve adequate technical success and limb salvage with minimal complications, which goes against the perceived notion that the organized nature of such emboli makes them less likely to respond to lytic therapy. ER may therefore be a viable option for patients with an AF embolus who are at high risk for surgery or have hostile anatomy.

In addition to the higher incidence of postoperative complications, there was also a significantly higher mortality with OR at all time points. Although the overall 30-day mortality rate in ER patients (5.44%) is comparable to that in the STILE[1] and TOPAS[2] trials (4.3% and 8.8%, respectively), the corresponding rate in the OR group (13.18%) is remarkably higher than in the STILE (5.1%) or TOPAS (5.9%) trials. This might be attributed to the higher prevalence of comorbidities in our patient population, with a higher prevalence of coronary artery disease, hypertension, congestive heart failure, cancer, and hypercholesterolemia. What is clear is that the perioperative morbidity and mortality with OR continue to be high in contemporary practice for patients treated for ALI, despite aggressive medical management and cardiovascular risk reduction strategies. This has to be considered in the decision-making algorithm, perhaps favoring ER despite its lower technical success but improved safety profile and similar limb salvage rate compared with OR.

Another important observation is that the only consistent predictor for all adverse outcomes in our study was the presentation with irreversible limb ischemia (Rutherford III ischemia). As expected, the technical success in this group of patients was poor, and even when the revascularization was initially successful, the increased risk of loss of primary patency, major amputation, and death observed negates any likelihood of salvaging a functional limb in those patients. Consequently, for patients presenting with advanced Rutherford III ALI, any type of revascularization might be futile or even harmful, given the life-threatening consequences of the reperfusion syndrome, suggesting that a primary amputation should be considered a potentially safer alternative.

This study, being retrospective, has important limitations that can affect the completeness of the available perioperative and follow-up data. In addition, we tried to mitigate the pitfall of the uneven distribution of the patients among the severity groups by focusing on Rutherford II patients in our comparisons. This yielded an even distribution of Rutherford IIa and IIb patients treated with OR but a higher number of IIa patients treated with ER, which could still introduce a selection bias. Although this subgroup analysis was aimed at analyzing comparable groups, it resulted in exclusion of patients with extremes of ischemic class on presentation. This, however, mirrors the strategy used in randomized trials for ALI that included only patients with Rutherford II ischemia.

CONCLUSIONS

Despite the limitations, we believe that the large sample size, the subgroup analyses, and the regression models allow us to conclude that OR as an initial treatment of ALI results in improved technical success rates in patients with Rutherford II ischemia, especially when it is caused by a failed stent or bypass graft. This was at the expense of a higher mortality rate compared with ER, without the added advantage of improved patency or limb salvage at 30 days and at 1 year.

In patients with Rutherford II ischemia secondary to stent failure or native artery thrombosis, the observed trend toward improved limb salvage with thrombolysis (at 30 days and 1 year) might suggest that ER may be considered the initial treatment for this particular group of patients. In contrast, patients with failed bypass grafts had a trend toward improved limb salvage with OR, which might suggest that surgery should be the preferred initial treatment for those patients. However, the decision between OR and ER has to be individualized on the basis of not only the class and etiology of ischemia but, more important, the patient's comorbidities, given the increased mortality associated with open repair.

AUTHOR CONTRIBUTIONS

Conception and design: AT, RC
Analysis and interpretation: AT, RB, EA, LM, MM, RC
Data collection: AT, RB, RC
Writing the article: AT, RC
Critical revision of the article: AT, RB, EA, LM, MM, RC
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